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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : A61K 51/12 — A1

(11) International Publication Number: **WO 00/29034**

(43) International Publication Date: 25 May 2000 (25.05.00)

(21) International Application Number: PCT/GB99/03774

(22) International Filing Date: 12 November 1999 (12.11.99)

(30) Priority Data:

60/108,121	12 November 1998 (12.11.98)	US
9900824.5	14 January 1999 (14.01.99)	GB

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(81) Designated States: AE, AL, AM, AT, AT (Utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), DM, EE, EE (Utility model), ES, FI, FI (Utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PRODUCTS AND METHODS

(57) Abstract

Radioactive sources suitable for use in brachytherapy comprising one or more insoluble salts, wherein the insoluble salt contains, or the insoluble salts together contain, at least two different radioisotopes. Preferred radioisotopes are ^{103}Pd and ^{125}I and preferred insoluble salts include $^{103}Pd(^{125}I_2)$, $^{103}Pd^{35}S$, $^{89}Sr^{32}PO_4$ and $^{89}Sr^{35}SO_4$.

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Products and Methods

This invention relates to radiotherapy. More particularly, it relates to radioisotopes and radioactive sources for use in brachytherapy.

Brachytherapy is a general term covering medical treatment which involves the temporary or permanent implantation or insertion of a radioactive source into the body of a patient. The radioactive source is thereby located close to the area of the body which is being treated. This has the advantage that a high dose of radiation may be delivered to the treatment site with relatively low dosages of radiation to surrounding healthy tissue.

Brachytherapy has been proposed for use in the treatment of a variety of conditions, including arthritis and cancer, for example breast, brain, liver and ovarian cancer and especially prostate cancer in men (see for example J.C. Blasko et al., *The Urological Clinics of North America*, 23, 633-650 (1996), and H. Ragde et al., *Cancer*, 80, 442-453 (1997)). Prostate cancer is the most common form of malignancy in men in the USA, with more than 44,000 deaths in 1995 alone. Treatment may involve the temporary implantation of a radioactive source for a calculated period, followed by its removal. Alternatively, the radioactive source may be permanently implanted in the patient and left to decay to an inert state over a predictable time. The use of temporary or permanent implantation depends on the isotope selected and the duration and intensity of treatment required.

Permanent implants for prostate treatment comprise radioisotopes with relatively short half lives and lower energies relative to temporary sources. Examples of permanently implantable sources include iodine-125 or palladium-103 as the radioisotope. The radioisotope is generally encapsulated in a titanium casing to form a "seed" which is then implanted. Temporary implants for the treatment of prostate cancer may involve iridium-192 as the radioisotope.

Recently, brachytherapy has also been proposed for the treatment of restenosis (for reviews see R. Waksman, *Vascular Radiotherapy Monitor*, 1998, 1, 10-18, and *MedPro Month*, January 1998, pages 26-32). Restenosis is a renarrowing of the blood vessels after initial treatment of coronary artery disease.

Coronary artery disease is a condition resulting from the narrowing or blockage of the coronary arteries, known as stenosis, which can be due to many factors including the formation of atherosclerotic plaques within the arteries. Such blockages or narrowing may be treated by mechanical removal of the plaque or by insertion of stents to hold the artery open. One of the most common forms of treatment is percutaneous transluminal coronary angioplasty (PTCA) - also known as balloon angioplasty. At present, over half a million PTCA procedures are performed annually in the USA alone. In PTCA, a catheter having an inflatable balloon at its distal end is inserted into the coronary artery and positioned at the site of the blockage or narrowing. The balloon is then inflated which leads to flattening of the plaque against the artery wall and stretching of the artery wall, resulting in enlargement of the intraluminal passage way and hence increased blood flow.

PTCA has a high initial success rate but 30-50% of patients present themselves with stenotic recurrence of the disease, i.e. restenosis, within 6 months. One treatment for restenosis which has been proposed is the use of intraluminal radiation therapy. Various isotopes including iridium-192, strontium-90, yttrium-90, phosphorous-32, rhenium-186 and rhenium-188 have been proposed for use in treating restenosis.

Conventional radioactive sources for use in brachytherapy include so-called seeds, which are sealed containers, for example of titanium, containing the radioisotope within a sealed chamber but permitting radiation to exit through the container/chamber walls. Such seeds are only suitable for use with radioisotopes which emit radiation which can penetrate the chamber/container walls. Therefore, such seeds are generally used with radioisotopes which emit γ-radiation or low-energy X-rays, rather than with β-emitting radioisotopes.

Solutions of radioactive isotopes inside a catheter balloon have also been proposed for use in the treatment of restenosis (US 5616114). However, the use of radioactive liquids increases the risks involved with the procedure due to the possibility of leakage of the radioactive material either inside the patient or when the catheter is being transported, stored or set up.

Given the increasing importance of brachytherapy, there is a need for a wide range of suitable radiation sources to be readily available, to allow flexibility in matching a source to the required treatment. Such sources should preferably limit the risk of exposure of healthy tissue in the patient to radiation if, for example, the

radioisotope is exposed directly to body fluids either accidentally or when in use.

WO97/49335 proposes insoluble radioactive pyrophosphate salts for use in brachytherapy. There is a limited range of suitable insoluble pyrophosphate salts available. Phosphorus-32 is a β-emitter and hence salts comprising ^{32}P are not suitable for use in conventional sealed sources, for example metal seeds, where the wall of the container will absorb most of the radiation emitted.

Radioactive seeds comprising a coating of silver iodide on a silver wire are known (US-A 4323055). Such seeds are formed by chloriding or bromiding the silver to form a layer of silver chloride or bromide, and then replacing the chloride or bromide with radioactive iodide ions by ion exchange.

We now believe that significant advantages attach to the use of radiation sources comprising insoluble salts of radioactive ions in brachytherapy. Such salts are to be preferred for use in brachytherapy as they will not generally solubilize in blood or other bodily fluids and therefore the risk of the release of such salts into the circulation in the body is reduced. Accidental exposure of patients or medical staff to undesirable radiation will therefore be less likely. Radioactive sources comprising insoluble salts are also generally safer and easier to manufacture.

It would also be advantageous if radioactive sources for use in brachytherapy comprising two or more different radioisotopes were readily available, as this would allow use of sources emitting more than one type of radiation and/or radiation of different energies, tailored if desired to the particular treatment required.

US-A 3663685 discloses radioactive materials for use in brachytherapy which comprise a water-insoluble carrier for radioisotopic ions dispersed in a water-insoluble vehicle. The radioisotope ion may form part of the carrier, for example as the anion or cation of a salt. However there is no mention that more than one radioisotope could be used in the radioactive materials.

US-A 5674177 discloses vascular implants including a first nuclide species which has a half life in the range of 7 hours to 7 days and a second nuclide species which has a half life of more than 100 days. The nuclide species are formed by suitable irradiation of a metal alloy and the first nuclide species preferably decays into the second nuclide species. There is no suggestion that the nuclides be comprised in one or more insoluble salts.

According to one aspect of the invention there is therefore provided a radioactive source for use in brachytherapy, preferably a sealed source, comprising one or more insoluble salts wherein the insoluble salt(s) together contain at least two different radioisotopes with the proviso that when the source comprises a single insoluble salt then said salt is not a pyrophosphate salt.

The radioactive sources of the invention may also comprise a suitable non-radioactive support for the insoluble salt(s). Suitable support materials include plastics, graphite, zeolites, ceramics, glass, metals, polymer matrices, ion-exchange resins or other, preferably porous, materials. Preferably, such support materials are inert and biocompatible, and will not react with the insoluble salt(s) but merely provide a surface onto which the salt(s) may be immobilised. The support material may be in the form of a bead, wire or rod. The wires or rods

be in the form of a bead, wire or rod. The wires or rods will preferably be X-ray dense e.g. of silver, tungsten, gold or lead.

The radioactive sources of the invention may also comprise a hollow sealed container encapsulating the insoluble salt(s) either with or without a support. Such containers should be biocompatible. Titanium or stainless steel are suitable materials for such containers, or some other material which is corrosion resistant, compatible with body fluids and non-toxic, and which does not unduly absorb the radiation emitted from the radioisotope(s). Titanium is a preferred material for the container.

While conventional seeds use a titanium container welded at both ends, it is not essential that this be the case in the present invention. For the majority of β-emitting radionuclides to be effective in brachytherapy when in a sealed container (i.e. as a sealed source or device), the container should not block the therapeutical β-particle emissions. Such containers could for example comprise titanium seeds with a thinner wall thickness, other metals with cross-sections which minimise β-particle capture, or polymeric containers which are not biodegradable within the lifetime of the radionuclide. Any of the supports or carriers mentioned above could also comprise sealed sources by overcoating with a lacquer or varnish that would be tolerable in vivo, yet would allow β-radiation to interact with the desired tissues. Under such particular circumstances, i.e. when containers are employed which are sufficiently β-particle transparent, the use of pyrophosphates may fall within the scope of the present invention.

Particles of the insoluble salt(s) may be incorporated within a sealed source, such as a polymer

matrix, glass, or a plastic and/or ceramic composite, or a contained source such as a matrix or part of a matrix or the centre of a matrix in which the salt(s) are enclosed within a container that is not necessarily sealed. If the salt(s) are enclosed within a polymer matrix, this may subsequently be plated.

Preferably, the support and/or the container are formed of an X-ray dense material, such that the sources may be more readily located by X-ray imaging techniques during or following implantation or insertion into a patient.

The source should be of a size and dimension suitable for its intended use. Seeds for use in the treatment of prostate cancer are, for example, typically substantially cylindrical in shape and approximately 4.5mm long with a diameter approximately 0.8mm and are of such a shape that they may be delivered to the treatment site using a hypodermic needle. For use in the treatment of restenosis, a source should be of suitable dimensions to be inserted inside a coronary artery, for example with a length of 10mm and a diameter of 1mm, preferably a length of 5mm and a diameter of 0.8mm and most preferably with a length of 3mm and a diameter of 0.6mm.

Preferred insoluble salts are salts comprising one or more of ^{125}I, ^{103}Pd, ^{89}Sr, ^{35}S and ^{32}P, for example strontium phosphate, carbonate or sulphate and palladium oxide, hydroxides, iodide or bromide.

By way of example, some radionuclides of interest for inclusion in the sources of the invention, especially sealed sources, include the following:

Radionuclide	half life (days)	emission type	energy (MeV)	pathlength (microns)
Phosphorus				
32	14.282	beta	1.71	2.7
33	25.3	beta	0.25	
Iodine				
123	0.52	gamma	0.159	
		X-ray	Te-x	
125	60.14	gamma	0.035	
		X-ray	Te-x	
131	8.0	beta	0.607, 0.336	0.42
		gamma	0.283, 0.364, 0.637, 0.723	
		X-ray	Xe-x	
Palladium				
103	16.97	gamma	0.270, 0.296	
		X-ray	Rh-x	
109	0.52	beta	1.028	
		gamma	0.088, 0.311, 0.636	
		X-ray	Ag-x	
Yttrium				
90	2.67	beta	2.288	3.9
		gamma	2.186	
91	58.8	beta	1.545	
		gamma	1.21	
Gold				
198	2.69	beta	1.371	
		gamma	0.412, 0.676	
199	3.14	beta	0.296, 0.250, 0.462	
		gamma	0.158, 0.208	
		X-ray	Hg-x	

It may be seen that a variety of emission types (i.e., beta particle, alpha particle, gamma rays, X-rays) are available and that the energy levels of the various emissions range from less than 0.1 MeV to over 2.0 MeV. Thus, an advantage may be gained in mixing different emission types and energies.

Insoluble salts of most ions can be made using a suitable counter-ion. For the purposes of the invention a salt is considered to be insoluble if its solubility product constant is lower than about 1×10^{-5}, preferably less than about 1×10^{-10} and most preferably less than 1×10^{-16}.

The radioisotopes in the insoluble salt(s) may be in a cation, an anion or both. The radioisotopes may be in a complex ion optionally comprising one or more other radioisotopes. Suitable radioactive complex ions include $^{32}PO_4^{2-}$ and $^{35}SO_4^{2-}$. Two or more different radioisotopes may be present in a single insoluble salt or a mixture of different salts may be used, two or more of which contain different radioisotopes. For example, if ^{103}Pd and ^{125}I are the radioisotopes, then they may be present as $^{103}Pd(^{125}I)_2$ or as a mixture of a salt containing palladium-103 with a cold anion (e.g. bromide) and a salt containing iodine-125 and a cold cation (e.g. silver). A source comprising both ^{103}Pd and ^{125}I would provide a short intense radioactivity due to the ^{103}Pd and a longer, lower activity due to the ^{125}I.

Two or more radioisotopes may be present as cations or anions in a single salt. Two or more radioisotopes may also be present in the anions or cations of different salts which have the same counterion (e.g. $^{89}SrPO_4$ and $^{51}CrPO_4$). The sources and insoluble salts of the invention

may also contain 2 or more different radioisotopes of a single element (e.g. ^{131}I and ^{125}I).

Additionally, one of the two or more radioisotopes in the salt(s) could be suitable for radio imaging (i.e., gamma imaging). For example, in the salt $^{111}In_2{}^{35}S_3$, ^{111}In could be used as a radio imaging agent. In an alternative example, the salt ^{99m}TcS is well known for its imaging properties but has no therapeutic effect. Combining a radioactive isotope with ^{99m}Tc (e.g. in $^{99m}Tc^{35}S$) would provide an agent with both therapeutic and imaging properties.

Preferably, the different radioisotopes emit different types or energies of radiation (e.g. alpha, beta, gamma, X-rays etc.), or have different half-lives. Preferred insoluble salts are salts comprising two or more of ^{125}I, ^{103}Pd, ^{89}Sr, ^{32}P (for example as a phosphate) and ^{35}S (for example as the sulfate or sulfide). Especially preferred insoluble salts are $^{103}Pd(^{125}I)_2$, $^{103}Pd^{35}S$, $^{89}Sr^{32}PO_4$ and $^{89}Sr^{35}SO_4$. Such salts form a further aspect of the invention. Other therapeutically useful isotopes include but are not necessarily limited to the following: ^{117m}Sn, ^{131}I, ^{132}I, ^{47}Sc, ^{67}Cu, ^{186}Re, ^{153}Sm, ^{177}Lu, ^{166}Ho, ^{212}Bi, ^{255}Fm, ^{90}Y.

The radioactive sources of the invention may also comprise cold isotopes corresponding to the radioisotopes. Thus the insoluble salts of the sources of the invention may contain both "hot" (i.e. radioactive) and "cold" (i.e. non-radioactive) isotopes of an element. Dilution of the radioisotopes with corresponding cold isotopes is one method whereby the overall activity of the sources of the invention may be altered or controlled as desired.

The table below shows the solubility product constants for a number of salts we have identified for use as insoluble salts according to the invention (values taken from The Handbook of Chemistry and Physics, 74th Ed., 1993-1994, section 8, page 49, Lange's Handbook of Chemistry, 14th ed. 1992, section 8, pp 6-11 or other literature). This list is clearly not limiting.

Compound	Ksp	Possible Salts
Bismuth Sulfide	1.82 x 10(-99)	$^{212}Bi_2{}^{35}S_3$, $^{210}Bi_2{}^{35}S_3$
Bismuth Iodide	8.1 x (10(-19)	$^{212}Bi^{125}I_3$, $^{212}Bi^{131}I_3$, $^{210}Bi^{125}I_3$
Bismuth Phosphate	1.3 x 10(-23)	$^{212}Bi^{32}PO_4$, $^{210}Bi^{32}PO_4$
Cadmium Phosphate	2.5 x 10(-33)	$^{109}Cd_3(^{32}PO_4)_2$
Cadmium Sulfide	8.0 x 10(-26)	$^{109}Cd^{35}S$
Chromium Phosphate (green)	2.4 x 10(-23)	$^{51}Cr^{32}PO_4.4H_2O$
Chromium Phosphate (violet)	1.0 x 10(-17)	$^{51}Cr^{32}PO_4.4H_2O$
Copper(I) Iodide	1.27 x 10(-12)	$^{64}Cu^{125}I$, $^{67}Cu\ ^{131}I$
Copper(I) Sulfide	2.26 x 10(-48)	$^{64}Cu_2{}^{35}S$
Copper(II) Iodate	7.4 x 10(-8)	$^{64}Cu(^{131}IO_3)_2$, $^{67}Cu(^{125}IO_3)_2$
Copper(II) Sulfide	6.0 x 10(-37)	$^{64}Cu\ ^{35}S$
Gold(I) Iodide	2.0 x 10(-13)	$^{198}Au^{131}I$, $^{198}Au^{125}I$, $^{199}Au^{125}I$
Gold(III) Iodide	1.0 x 10(-46)	$^{198}Au^{131}I_3$, $^{198}Au^{125}I_3$, $^{199}Au^{125}I_3$
Indium Sulfide	5.7 x 10(-74)	$^{111}In_2{}^{35}S_3$
Lead Sulfide	3.0 x 10(-28)	^{209}Pb,^{35}S, $^{210}Pb^{35}S$, $^{212}Pb\ ^{35}S$
Lead Sulfate	1.6 x 10(-8)	$^{212}Pb^{35}SO_4$
Lead Hydrogen Phosphate	1.3 x 10(-10)	$^{212}PbH^{32}PO_4$
Lead Phosphate	8.0 x 10(-43)	$^{212}Pb_3(^{32}PO_4)_2$
Lead Iodide	7.1 x 10(-9)	$^{212}Pb^{131}I_2$, $^{212}Pb^{125}I_2$
Lead Chromate	2.8 x 10(-13)	$^{212}Pb^{51}CrO_4$
Manganese(II) Sulfide	3.0 x 10(-14)	$^{54}Mn\ ^{35}S$, $^{56}Mn\ ^{35}S$
Mercury(I) iodide	5.33 x 10(-29)	$^{197m}Hg_2{}^{125}I_2$, $^{197m}Hg_2\ ^{131}I_2$
Mercury(I) Iodate	2.0 x 10(-14)	$^{197m}Hg_2(^{131}IO_3)_2$, $^{197m}Hg_2(^{125}IO_3)_2$
Mercury(II) iodide	2.82 x 10(-29)	$^{197m}Hg^{125}I_2$, $^{197m}Hg^{131}I_2$, $^{197}Hg^{125}I_2$
Palladium(II) sulfide	2.03 x 10(-58)	^{103}Pd, ^{35}S
Strontium Sulfite	4.0 x 10(-8)	$^{89}Sr^{35}SO_3$, $^{85}Sr\ ^{35}SO_3$
Strontium Sulfate	3.2 x 10(-7)	$^{89}Sr^{35}SO_4$, $^{85}Sr\ ^{35}SO_4$
Strontium Iodate	3.3 x 10(-7)	$^{89}Sr(^{125}IO_3)_2$, $^{89}Sr(^{131}IO_3)_2$
Strontium Phosphate	4.0 x 10(-28)	$^{89}Sr_3(^{32}PO_4)_2$
Thallium Chromate	1.0 x 10(-12)	$^{201}Tl_2{}^{51}CrO_4$
Thallium Sulfide	5.0 x 10(-21)	$^{201}Tl_2{}^{35}S$
Tin(II) sulfide	1.00 x 10(-26)	$^{117m}Sn^{35}S$, $^{113}Sn\ ^{35}S$, $^{125}Sn\ ^{35}S$
Zinc Sulfide	2.0 x 10(-25)	$^{65}Zn^{35}S$
Zinc Phosphate	9.0 x 10(-33)	$^{65}Zn_3(^{32}PO_4)_2$
Zinc Iodate	2.0 x 10(-8)	$^{65}Zn(^{125}IO_3)_2$, $^{65}Zn(^{131}IO_3)_2$

Other suitable salts include barium sulphate (K_{sp} = 1 x 10^{-7}), palladium oxide, palladium bromide and palladium iodide (D.E. Horner et al., South Eastern regional meeting of American Chemical Society on biological aspects of liquid chromatography, Conf-761002-4, 27 Oct. 1976). In addition to these insoluble radioactive salts, others such as $^{90}Y^{32}PO_4$ may be used. These combinations are useful for therapeutic situations where different dose rates, energies, and types of energies are required (i.e. mixed gamma, beta, or alpha radiation). Also, a combination could afford a therapeutic isotope together with an imaging isotope for improved detection of the device/source after implantation.

As a further feature of the invention there is provided a method for the preparation of an insoluble radioactive salt suitable for use in brachytherapy, said salt comprising two or more different radioisotopes, said method comprising the steps of

a) providing a solution containing a suitable cation,

b) providing a solution containing a suitable anion,

c) mixing the solutions of the cation and the anion together such that precipitation of an insoluble radioactive salt occurs.

As a further feature of the invention there is provided a method for the preparation of a radioactive source for use in brachytherapy comprising one or more insoluble salts wherein the insoluble salt(s) together contain at least two different radioisotopes, the method comprising

a) providing a solution containing one or more anions,

b) providing a solution containing one or more cations,

the anions and cations of steps a) and b) together comprising at least two different radioisotopes, and

c) mixing together the solutions of the anion(s) and the cation(s) such that precipitation of one or more insoluble salts containing the radioisotopes occurs.

In step c) of either method, a support onto which the insoluble salt(s) may precipitate may optionally be present. Suitable supports for use in the above method include graphite, zeolites, ion exchange resins, ceramics, plastics, polymer matrices or other, preferably porous, materials on which a salt will form. The support may be in the form of a bead, rod, filament or wire. Such supports may then be encapsulated, for example inside a container to form a sealed source, or by plating with a suitable metal, for example silver.

In one embodiment of the methods, a polymer matrix support in particulate form is saturated with a suitable anion or cation by equilibration in a solution thereof, washed if desired, followed by treatment with a solution containing a suitable insoluble-salt-forming cation or anion which results in precipitation of an insoluble salt on the surface of or within pores of the polymer matrix. Such a matrix may itself then be encapsulated, for example within a metal or further polymer or plastics coating if desired.

Together, the cation(s) and the anion(s) will comprise two or more different radioisotopes. The anion(s) and cation(s) may be complex ions. The insoluble

salt(s) may comprise more than two radioisotopes. Depending on the desired level of activity of any radioactive source comprising a radioactive salt prepared according to the method of the invention, the solutions of the anion(s) and/or cation(s) may also comprise "cold" anions or cations corresponding to the anions or cations comprising radioisotopes.

The cation(s) and anion(s) used in the method(s) of the invention are chosen such that together they form an insoluble salt or salts. The counter-ions present in the initial solutions of the anion(s) and cation(s) should preferably be chosen such that they will not form any insoluble salt(s) themselves when the solutions are mixed. The counter-ions therefore suitably remain in solution whilst the insoluble salt(s) precipitates out. The salt(s) can then be filtered off or the solution decanted.

If it is desired to encapsulate the insoluble salt inside a sealed container, the mixing of the two solutions can occur inside the container prior to sealing. For example, an aliquot of a palladium-103 chloride solution ($^{103}PdCl_2$) may be placed inside an empty metal container followed by an excess of a solution of sulfide (^{35}S), for example as the sodium salt, to form insoluble $^{103}Pd^{35}S$ inside the container, followed by welding shut of the container to form a sealed source or "seed".

Alternatively, the anion used may be hydroxide, for example in the form of an excess of sodium hydroxide solution, to lead to precipitation of palladium-103 hydroxide. Similarly, an excess of silver nitrate solution and a solution of sodium iodide (comprising ^{125}I or ^{131}I) may be used to precipitate a radioactive silver iodide salt.

As a further embodiment of the invention there is provided a method for the preparation of a radioactive source for use in brachytherapy comprising an insoluble radioactive salt, said salt comprising an anion and a cation, the anion and cation together containing two or more different radioisotopes, said method comprising the steps of

a) adsorbing either the cation or the anion on the surface of a suitable support,

b) contacting the support with a solution containing the other of the cation or the anion, whereby the insoluble salt forms on the surface of said support, and

c) optionally removing excess solution.

Suitable supports for use in the above method include graphite, zeolites, ion exchange resins, ceramics, polymer matrices, plastics or other, preferably porous, materials on which a salt will form. The support may be in the form of a bead, rod, filament or wire. Such supports may then be encapsulated, for example inside a container to form a sealed source.

The radioactivity levels of the sources produced using the methods of the invention may be altered or controlled as desired through variation of a number of parameters, including choice of radioisotopes, by dilution of the radioisotopes in the insoluble salts with "cold" isotopes and/or by choice of the size and surface area of the support.

The sources of the invention may be employed in brachytherapy using known methods of implantation or

insertion, as described for example in R. Waksman, *Vascular Radiotherapy Monitor*, 1998, 1, 10-18 and references therein, and in J.C. Blasko et al, *Endocuriether/Hypertherm Oncol*, 3, 131-9, (1987) and H. Ragde et al, *J Endourol*, 3, 209-18, (1989).

In a further aspect, the invention also provides a method of treatment of a condition which is responsive to radiation therapy, for example cancer, arthritis or restenosis, which comprises the temporary or permanent placement of a radioactive source comprising one or more insoluble salt(s) wherein the insoluble salt(s) together contain at least two different radioisotopes, at the site to be treated within a patient for a sufficient period of time to deliver a therapeutically effective dose. Preferably, the radioisotopes emit different types or energies of radiation selected from the group consisting of α, β, γ and X-ray radiation, or have different half-lives.

Preferably, the methods of treatment of the invention are employed for the treatment of prostate cancer or to inhibit restenosis at a site within the vascular system of a patient which has previously been subjected to PTCA.

The following Examples are non-limiting illustrations of the invention. In all the Examples, the ions in the insoluble salts may be replaced by ions comprising an equivalent radioisotope to give radioactive salts. The radioactive ion may be the cation, the anion or both. For example, the strontium used may comprise ^{90}Sr, the palladium used may comprise ^{103}Pd, the phosphate used may comprise ^{32}P, the iodide used may comprise ^{125}I and the sulfate used may comprise ^{35}S. A portion of the cations and/or anions used in the Examples of the invention may also be replaced by different ions to give mixtures of more than one insoluble salt.

Examples

Example 1
Production of Strontium Phosphate Coated PVA Particles

Twenty milliliters of 0.5M solution of strontium chloride ($SrCl_2$) was added to one gram of 50 to 150μm polyvinyl alcohol particles (PVA) and rotated for one hour. The mixture was then placed into a 150-ml beaker with a stir bar. The excess solution was decanted off, leaving the particles still slightly wet. Thirty-five milliliters of 0.5M sodium phosphate (Na_2HPO_4) solution was then added and the mixture was stirred for fifteen minutes. The product was filtered and thoroughly rinsed through a 100 mesh metal screen with water and finally nanopure water. The particles were then bottled in nanopure water.

The initial PVA particles were white. The expected product of the reaction was also white. Thus, a color change within the process was neither expected or observed. Optical microscopy was done on the sample in order to determine if coating occurred. The uncoated PVA particles appeared crystalline and fairly transparent.

The coated particles were much more opaque. Inductively coupled plasma analysis of the coated particles determined a strontium concentration of 8.5 mg/gram of PVA.

The resulting strontium phosphate coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

Example 2
Production of Strontium Sulfate Coated PVA Particles

Twenty milliliters of 0.5M solution of strontium chloride ($SrCl_2$) was added to one gram of 50 to 150μm polyvinyl alcohol particles (PVA) and rotated for one hour. The mixture was then placed into a 150-ml beaker with a stir bar. The excess solution was decanted off, leaving the particles still slightly wet. Thirty-five milliliters of 0.5M sodium sulfate (Na_2SO_4) solution was then added and the mixture was stirred for fifteen minutes. The product was filtered and thoroughly rinsed through a 100 mesh metal screen with water and finally nanopure water. The particles were then bottled in nanopure water.

The initial PVA particles were white. The expected product of the reaction was also white. Thus, a color change within the process was neither expected or observed. Optical microscopy was done on the sample in order to determine if coating occurred. The uncoated PVA particles appeared crystalline and fairly transparent. The coated particles were much more opaque.

The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

Example 3
Production of Strontium Carbonate Coated PVA Particles

Twenty milliliters of 0.5M solution of strontium chloride ($SrCl_2$) was added to one gram of 50 to 150μm polyvinyl alcohol particles (PVA) and rotated for one hour. The mixture was then placed into a 150-ml beaker with a stir bar. The excess solution was decanted off, leaving the particles still slightly wet. Thirty-five milliliters of 0.5M sodium carbonate (Na_2CO_3) solution was then added and the mixture was stirred for fifteen minutes. The product was filtered and thoroughly rinsed through a 100 mesh metal screen with water and finally nanopure water. The particles were then bottled in nanopure water.

The initial PVA particles were white. The expected product of the reaction was also white. Thus, a color change within the process was neither expected nor observed. Optical microscopy was done on the sample in order to determine if coating occurred. The uncoated PVA particles appeared crystalline and fairly transparent. The coated particles were much more opaque.

The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

Example 4
Production of Palladium Oxide Coated PVA Particles

Twenty milliliters of a saturated solution of palladium chloride ($PdCl_2$) was added to one gram of 50 to 150μm polyvinyl alcohol particles (PVA) and rotated overnight. The mixture was then placed into a 150-ml beaker with a stir bar. The excess solution was decanted

off, leaving the particles still slightly wet. Thirty-five milliliters of 0.5M sodium hydroxide (NaOH) solution was then added and the mixture was stirred for fifteen minutes. The product was filtered and thoroughly rinsed through a 100 mesh metal screen with water and finally nanopure water. The particles were then bottled in nanopure water.

After rotating overnight, the particles turned from white to dark brown. The addition of sodium hydroxide then caused the particles to turn a brownish black. The pH of the decanted solution before the addition of sodium hydroxide was 1.04. The pH of the final rinsed product was 10.48. Palladium hydroxide is expected to be a brown/black color, indicating a successful reaction.

The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

Example 5
Production of Palladium Iodide Coated PVA Particles (Method 1)

Twenty milliliters of a saturated solution of palladium chloride ($PdCl_2$) was added to one gram of 50 to 150μm polyvinyl alcohol particles (PVA) and rotated for one hour. The particles were filtered and thoroughly rinsed through a 100 mesh metal screen with water. The mixture was then placed into a 150-ml beaker with a stir bar. The excess solution was decanted off, leaving the particles still slightly wet. Fifteen milliliters of 0.5M potassium iodide (KI) solution was then added and the mixture was stirred for fifteen minutes. The product was filtered and thoroughly rinsed through a 100 mesh metal

screen with water and finally nanopure water. The particles were then bottled in nanopure water.

After rotating for one hour, the particles turned from white to medium brown due to adsorption of palladium ions onto the PVA particles. The addition of potassium iodide then caused the particles to turn a purplish black as expected for formation of palladium iodide. Inductively coupled plasma analysis determined the palladium concentration to be 12.2 mg/gram PVA.

The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

Example 6
Production of Palladium Bromide Coated PVA Particles

Twenty milliliters of a saturated solution of palladium chloride ($PdCl_2$) was added to one gram of 50 to 150μm polyvinyl alcohol particles (PVA) and rotated for one hour. The particles were filtered and thoroughly rinsed through a 100 mesh metal screen with water. The mixture was then placed into a 150-ml beaker with a stir bar. The excess solution was decanted off, leaving the particles still slightly wet. Thirty-five milliliters of 0.5M potassium bromide (KBr) solution was then added and the mixture was stirred for fifteen minutes. The product was filtered and thoroughly rinsed through a 100 mesh metal screen with water and finally nanopure water. The particles were then bottled in nanopure water.

After rotating for one hour, the particles turned from white to medium brown due to adsorption of palladium ions by the PVA particles. The addition of potassium bromide did not cause any change in color, however, the bromide salt is expected to be similar in color to the

starting palladium solution and hence the lack of color change was as expected.

The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

Example 7

Production of Palladium Iodide Coated PVA Particles (Method 2)

Twenty milliliters of 2% Iodine (I_2) in water was added to one gram of 50 to 150μm polyvinyl alcohol particles (PVA) and rotated for one hour. The particles were filtered and thoroughly rinsed through a 100 mesh metal screen with water. The mixture was then placed into a 150-ml beaker with a stir bar. The excess solution was decanted off, leaving the particles still slightly wet. Thirty-five milliliters of a saturated solution of palladium chloride ($PdCl_2$) was then added and the mixture was stirred for fifteen minutes. The product was filtered and thoroughly rinsed through a 100 mesh metal screen with water and finally nanopure water. The particles were then bottled in nanopure water.

After rotating for one hour, the particles turned from white to reddish black. The addition of palladium chloride then caused the particles to turn rusty black.

The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

Example 8
Production of Strontium Phosphate Coated Cation Exchange Resin

Twenty milliliters of 0.5M solution of strontium chloride ($SrCl_2$) was added to one gram of 16 to 40 mesh cation exchange resin and rotated for one hour. The resin was filtered and thoroughly rinsed through a 100 mesh metal screen with water. The mixture was then placed into a 150-ml beaker with a stir bar. The excess solution was decanted off, leaving the resin still slightly wet. Thirty-five milliliters of 0.5M sodium hydrogen phosphate (Na_2HPO_4) solution was then added and the mixture was stirred for fifteen minutes. The product was filtered and thoroughly rinsed through a 100 mesh metal screen with water and finally nanopure water. The resin was then bottled in nanopure water.

Both the cation exchange resin and the final product were gold. A color change within the process was not observed nor was precipitation of a thin layer of $SrPO_4$ expected to change the macroscopic color of the ion exchange resin. Inductively coupled plasma analysis determined the strontium concentration to be 25.7mg/gram of cation exchange resin.

The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

Example 9
Production of Strontium Carbonate Coated Cation Exchange Resin

Twenty milliliters of 0.5M solution of strontium chloride ($SrCl_2$) was added to one gram of 16 to 40 mesh

cation exchange resin and rotated for one hour. The resin was filtered and thoroughly rinsed through a 100 mesh metal screen with water. The mixture was then placed into a 150-ml beaker with a stir bar. The excess solution was decanted off, leaving the resin still slightly wet. Thirty-five milliliters of 0.5M sodium carbonate (Na_2CO_3) solution was then added and the mixture was stirred for fifteen minutes. The product was filtered and thoroughly rinsed through a 100 mesh metal screen with water and finally nanopure water. The resin was then bottled in nanopure water.

Both the cation exchange resin and the final product were gold. A color change within the process was not observed nor was precipitation of a thin layer of $SrCO_3$ expected to change the macroscopic color of the ion exchange resin.

The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

Example 10
Production of Strontium Sulfate Coated Cation Exchange Resin

Twenty milliliters of 0.5M solution of strontium chloride ($SrCl_2$) was added to one gram of 16 to 40 mesh cation exchange resin and rotated for one hour. The resin was filtered and thoroughly rinsed through a 100 mesh metal screen with water. The mixture was then placed into a 150-ml beaker with a stir bar. The excess solution was decanted off, leaving the resin still slightly wet. Thirty-five milliliters of 0.5M sodium sulfate (Na_2SO_4) solution was then added and the mixture was stirred for fifteen minutes. The product was filtered and thoroughly

rinsed through a 100 mesh metal screen with water and finally nanopure water. The resin was then bottled in nanopure water.

Both the cation exchange resin and the final product were gold. A color change within the process was not observed nor was precipitation of a thin layer of $SrSO_4$ expected to change the macroscopic color of the ion exchange resin.

The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

Example 11
Production of Palladium Iodide Coated Cation Exchange Resin (Method 1)

Twenty milliliters of a saturated solution of palladium chloride ($PdCl_2$) was added to one gram of 16 to 40 mesh cation exchange resin and rotated for one hour. The resin was filtered and thoroughly rinsed through a 100 mesh metal screen with water. The mixture was then placed into a 150-ml beaker with a stir bar. The excess solution was decanted off, leaving the resin still slightly wet. Thirty-five milliliters of 0.5M potassium iodide (KI) solution was then added and the mixture was stirred for fifteen minutes. The product was filtered and thoroughly rinsed through a 100 mesh metal screen with water and finally nanopure water. The particles were then bottled in nanopure water.

After rotating for one hour, the particles turned from gold to reddish brown. The addition of potassium iodide then caused the resin to turn black as expected due to formation of the insoluble salt palladium iodide. Inductively coupled plasma analysis determined the

palladium concentration to be 7.4 mg/gram of cation exchange resin.

The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

Example 12

Production of Palladium Bromide Coated Cation Exchange Resin

Twenty milliliters of a saturated solution of palladium chloride ($PdCl_2$) was added to one gram of 16 to 40 mesh cation exchange resin and rotated for one hour. The resin was filtered and thoroughly rinsed through a 100 mesh metal screen with water. The mixture was then placed into a 150-ml beaker with a stir bar. The excess solution was decanted off, leaving the resin still slightly wet. Thirty-five milliliters of 0.5M potassium bromide (KBr) solution was then added and the mixture was stirred for fifteen minutes. The product was filtered and thoroughly rinsed through a 100 mesh metal screen with water and finally nanopure water. The particles were then bottled in nanopure water.

After rotating for one hour, the particles turned from gold to reddish brown. The addition of potassium bromide then caused the resin to turn deep red as expected due to formation of the insoluble salt palladium bromide.

The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

Example 13
Production of Palladium Iodide Coated Cation Exchange Resin (Method 2)

Twenty milliliters of 2% iodine (I_2) in water was added to one gram of 16 to 40 mesh cation exchange resin and rotated for one hour. The resin was filtered and thoroughly rinsed through a 100 mesh metal screen with water. The mixture was then placed into a 150-ml beaker with a stir bar. The excess solution was decanted off, leaving the resin still slightly wet. Thirty-five milliliters of a saturated solution of palladium chloride ($PdCl_2$) was then added and the mixture was stirred for fifteen minutes. The product was filtered and thoroughly rinsed through a 100 mesh metal screen with water and finally nanopure water. The particles were then bottled in nanopure water.

After rotating for one hour, the particles turned from gold to red, but the color washed out after the first rinsing. The addition of palladium chloride then caused the resin to turn reddish brown.

The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

Example 14
Production of Palladium Oxide Coated Cation Exchange Resin

Twenty milliliters of a saturated solution of palladium chloride ($PdCl_2$) was added to one gram of 16 to 40 mesh cation exchange resin and rotated for one hour. The resin was filtered and thoroughly rinsed through a 100 mesh metal screen with water. The mixture was then placed into a 150-ml beaker with a stir bar. The excess solution

was decanted off, leaving the resin still slightly wet. Thirty-five milliliters of 0.5M sodium hydroxide (NaOH) solution was then added and the mixture was stirred for fifteen minutes. The product was filtered and thoroughly rinsed through a 100 mesh metal screen with water and finally nanopure water. The particles were then bottled in nanopure water.

After rotating for one hour, the particles turned from gold to reddish brown. The addition of sodium hydroxide then caused the resin to turn reddish black as predicted for the expected palladium oxide precipitate.

The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

Example 15
Production of Strontium Phosphate Coated Hydroxyapatite Particles

Twenty milliliters of 0.5M solution of strontium chloride ($SrCl_2$) was added to one gram of 40μm hydroxyapatite particles and rotated for one hour. The particles were filtered and thoroughly rinsed through a 500 mesh metal screen with water. The mixture was then placed into a 150-ml beaker with a stir bar. The excess solution was decanted off, leaving the particles still slightly wet. Thirty-five milliliters of 0.5M sodium hydrogen phosphate (Na_2HPO_4) solution was then added and the mixture was stirred for fifteen minutes. The product was filtered and thoroughly rinsed through a 500 mesh metal screen with water and finally nanopure water. The particles were then bottled in nanopure water.

Both the hydroxyapatite particles and the final product were white. A color change within the process was

neither expected nor observed. Optical microscopy was used to attempt to determine if any coating occurred. A visual difference between the uncoated hydroxyapatite particles and the final product could not be observed at low magnification. Inductively coupled plasma analysis determined the strontium concentration to be 5.8 mg/gram hydroxyapatite.

The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

Example 16

Production of Strontium Carbonate Coated Hydroxyapatite Particles

Twenty milliliters of 0.5M solution of strontium chloride (SrCl2) was added to one gram of 40μm hydroxyapatite particles and rotated for one hour. The particles were filtered and thoroughly rinsed through a 500 mesh metal screen with water. The mixture was then placed into a 150-ml beaker with a stir bar. The excess solution was decanted off, leaving the particles still slightly wet. Thirty-five milliliters of 0.5M sodium carbonate (Na_2CO_3) solution was then added and the mixture was stirred for fifteen minutes. The product was filtered and thoroughly rinsed through a 500 mesh metal screen with water and finally nanopure water. The particles were then bottled in nanopure water.

The initial hydroxyapatite particles were white. The expected product of the reaction was also white. Thus, a color change within the process was neither expected nor observed. Optical microscopy was used on the sample in an attempt to determine if coating occurred. No change could be determined at low magnification.

The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

Example 17
Production of Strontium Sulfate Coated Hydroxyapatite Particles

Twenty milliliters of 0.5M solution of strontium chloride ($SrCl_2$) was added to one gram of 40μm hydroxyapatite particles and rotated for one hour. The particles were filtered and thoroughly rinsed through a 500 mesh metal screen with water. The mixture was then placed into a 150-ml beaker with a stir bar. The excess solution was decanted off, leaving the particles still slightly wet. Thirty-five milliliters of 0.5M sodium sulfate (Na_2SO_4) solution was then added and the mixture was stirred for fifteen minutes. The product was filtered and thoroughly rinsed through a 500 mesh metal screen with water and finally nanopure water. The particles were then bottled in nanopure water.

Both the particles and the final product were white. A color change within the process was not observed either. Optical microscopy was used in an attempt to determine if any coating occurred. A difference between the uncoated hydroxyapatite particles and the final product could not be determined at low magnification.

The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

Example 18
Production of Palladium Oxide Coated Hydroxyapatite Particles (Method 1)

Twenty milliliters of a saturated solution of palladium chloride ($PdCl_2$) was added to one gram of 40μm hydroxyapatite particles and rotated for one hour. The particles were filtered and thoroughly rinsed through a 500 mesh metal screen with water. The mixture was then placed into a 150-ml beaker with a stir bar. The excess solution was decanted off, leaving the particles still slightly wet. Thirty-five milliliters of 0.5M sodium hydroxide (NaOH) solution was then added and the mixture was stirred for fifteen minutes. The product was filtered and thoroughly rinsed through a 500 mesh metal screen with water and finally nanopure water. The particles were then bottled in nanopure water.

After rotating for one hour, the particles turned from white to brown due to adsorption of the palladium onto the hydroxyapatite. The addition of sodium hydroxide caused the particles to turn dark brown as expected for the formation of the nearly black palladium oxide.

The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

Example 19
Production of Palladium Iodide Coated Hydroxyapatite Particles

Twenty milliliters of a saturated solution of palladium chloride ($PdCl_2$) was added to one gram of 40μm hydroxyapatite particles and rotated for one hour. The particles were filtered and thoroughly rinsed through a

500 mesh metal screen with water. The mixture was then placed into a 150-ml beaker with a stir bar. The excess solution was decanted off, leaving the particles still slightly wet. Thirty-five milliliters of 0.5M potassium iodide (KI) solution was then added and the mixture was stirred for fifteen minutes. The product was filtered and thoroughly rinsed through a 500 mesh metal screen with water and finally nanopure water. The particles were then bottled in nanopure water.

After rotating for one hour, the particles turned from white to brown. The addition of potassium iodide then caused the particles to turn dark brown as expected for the formation of the nearly black palladium iodide. Inductively coupled plasma analysis determined the palladium concentration to be 14.5 mg/gram hydroxyapatite.

The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

Example 20
Production of Palladium Bromide Coated Hydroxyapatite Particles

Twenty milliliters of a saturated solution of palladium chloride ($PdCl_2$) was added to one gram of 40μm hydroxyapatite particles and rotated for one hour. The particles were filtered and thoroughly rinsed through a 500 mesh metal screen with water. The mixture was then placed into a 150-ml beaker with a stir bar. The excess solution was decanted off, leaving the particles still slightly wet. Twenty-seven milliliters of 0.5M potassium bromide (KBr) solution was then added and the mixture was stirred for fifteen minutes. The product was filtered and thoroughly rinsed through a 500 mesh metal screen with

water and finally nanopure water. The particles were then bottled in nanopure water.

After rotating for one hour, the particles turned from white to brown. The addition of potassium bromide did not cause any further change in color as expected for formation of the deep red precipitate of palladium bromide.

The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

Example 21

Production of Palladium Oxide Coated Hydroxyapatite Particles (Method 2)

Twenty milliliters of a saturated palladium chloride ($PdCl_2$) was added to one gram of 40μm hydroxyapatite particles and rotated for one hour. The particles were filtered and thoroughly rinsed through a 500 mesh metal screen with nanopure water. The particles were then placed in a bottle, covered with aluminium foil and depyrogenated. Depyrogenation involves dry heat treatment at 240°C overnight. The dry particles were then bottled dry.

After rotating for one hour, the particles turned from white to brown. A further color change after depyrogenation was not observed.

The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

Example 22
Production of Palladium Iodide Coated PVA Particles Repeated with 10% w/w Pd Solution

Ten milliliters of a 10% w/w palladium chloride solution was added to 0.5 gram of 50 to 150μm polyvinyl alcohol particles (PVA) and rotated for over night. The particles were filtered and thoroughly rinsed through a 100 mesh metal screen with water. The mixture was then placed into a 150-ml beaker with a stir bar. The excess solution was decanted off, leaving the particles still slightly wet. Seventeen and half milliliters of 0.5M potassium iodide (KI) solution was then added and the mixture was stirred for twenty-five minutes. The product was filtered and thoroughly rinsed through a 100 mesh metal screen with water and finally nanopure water. The particles were then bottled in nanopure water.

After rotating for overnight, the particles turned from white to tan. The addition of potassium iodide then caused the particles to turn a reddish black as expected for formation of the insoluble palladium iodide.

The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

Example 23
Reverse Production of Palladium Iodide Coated Hydroxyapatite Particles

Twenty milliliters of 0.5M potassium iodide (KI) solution was added to one gram of 40μm hydroxyapatite particles and rotated for one hour. The particles were filtered and thoroughly rinsed through a 500 mesh metal screen with water. The mixture was then placed into a

150-ml beaker with a stir bar. The excess solution was decanted off, leaving the particles still slightly wet. Thirty-five milliliters of a saturated palladium chloride solution ($PdCl_2$) was then added and the mixture was stirred for fifteen minutes. The product was filtered and thoroughly rinsed through a 500 mesh metal screen with water and finally nanopure water. The particles were then bottled in nanopure water.

After rotating for one hour, the particles remained white. The addition of palladium chloride caused the particles to turn tan as would be expected for the formation of a small coating of the nearly black palladium iodide.

The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

Example 24
Reverse Production of Silver Iodide Coated Hydroxyapatite Particles

Twenty milliliters of 0.5M potassium iodide (KI) solution was added to one gram of 40μm hydroxyapatite particles and rotated for one hour. The particles were filtered and thoroughly rinsed through a 500 mesh metal screen with water. The mixture was then placed into a 150-ml beaker with a stir bar. The excess solution was decanted off, leaving the particles still slightly wet. Thirty-five milliliters of 0.5M silver nitrate ($AgNO_3$) solution was then added and the mixture was stirred for fifteen minutes. The product was filtered and thoroughly rinsed through a 500 mesh metal screen with water and finally nanopure water. The particles were then bottled in nanopure water.

After rotating for one hour, the particles remained white. The addition of silver nitrate caused the particles to turn yellowish green as expected for the formation of silver iodide on the particle surface.

The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

Example 25
Reverse Production of Strontium Phosphate Coated Hydroxyapatite Particles

Twenty milliliters of 0.5M sodium hydrogen phosphate (Na_2HPO_4) solution was added to one gram of 40μm hydroxyapatite particles and rotated for over night. The particles were filtered and thoroughly rinsed through a 500 mesh metal screen with water. The mixture was then placed into a 150-ml beaker with a stir bar. The excess solution was decanted off, leaving the particles still slightly wet. Thirty-five milliliters of 0.5M strontium chloride ($SrCl_2$) solution was then added and the mixture was stirred for fifteen minutes. The product was filtered and thoroughly rinsed through a 500 mesh metal screen with water and finally nanopure water. The particles were then bottled in nanopure water.

Both the hydroxyapatite particles and the final product were white. A color change within the process was neither observed nor expected.

The resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

Example 26
Production of Palladium Iodide-Silver Coated PVA Particles

One gram of palladium iodide coated PVA particles was pre-soaked in 8mM tin chloride ($SnCl_2$) solution for one hour. The treated particles were then rotated in twenty milliliters of 0.5M silver nitrate ($AgNO_3$) solution for three hours. The mixture was transferred to a 250 milliliter beaker and stirred. Fifty milliliters of 7% sodium carbonate (Na_2CO_3) solution was placed into a 150ml beaker and stirred. Fifty milliliters of a solution containing 0.72% of both silver nitrate ($AgNO_3$) and ammonium nitrate (NH_4NO_3); 0.66% tungstosilicic acid (TSA); and 1.31% formaldehyde was prepared. This solution was quickly added to the sodium carbonate solution. The mixture was then immediately added to the stirring particles. After fifteen minutes, 100 milliliters of 5% acetic acid was added. The particles were then thoroughly rinsed through a 100 mesh metal filter with water and then nanopure water. The particles were bottled in nanopure water.

No color change was observed until the mixture of the two solutions was added to the stirring light black particles (coated with PdI_2). Within five to ten minutes after this point, the stirring solution turned from crème brown to tan to grey and finally to black. The rinsed particles were black as expected for electrodeless deposition of metallic silver on top of the palladium iodide layer already on the particle surface. The resulting silver metal coated, palladium iodide containing PVA particles are suitable for use as brachytherapy sources for implantation or insertion in various tumours, in joints for relief of arthritis pain, and for prevention of restenosis. Alternatively the resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer

container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

Example 27
Production of Palladium Iodide-Silver Coated Ion Exchange Particles

One gram of palladium iodide coated ion exchange resin was pre-soaked in 8mM tin chloride ($SnCl_2$) solution for one hour. The treated resin was then rotated in twenty milliliters of 0.5M silver nitrate ($AgNO_3$) solution for three hours. The mixture was transferred to a 250 milliliter beaker and stirred. Fifty milliliters of 7% sodium carbonate (Na_2CO_3) solution was placed into a 150ml beaker and stirred. Fifty milliliters of a solution containing 0.72% of both silver nitrate ($AgNO_3$) and ammonium nitrate (NH_4NO_3); 0.66% tungstosilicic acid (TSA); and 1.31% formaldehyde was prepared. This solution was quickly added to the sodium carbonate solution. The mixture was then immediately added to the stirring resin. After fifteen minutes, 100 milliliters of 5% acetic acid was added. The resin was then thoroughly rinsed through a 100 mesh metal filter with water and then nanopure water. The resin was bottled in nanopure water.

No color change was observed until the mixture of the two solutions was added to the stirring black resin (coated with PdI_2). Within five to ten minutes after this point, the stirring solution turned from crème brown to tan to grey and finally to black as the silver metal was electrodelessly plated onto the ion exchange beads already coated with palladium iodide. The resulting silver metal coated, palladium iodide containing ion-exchange resin particles are suitable for use as brachytherapy sources for implantation or insertion in various tumours, in joints for relief of arthritis pain, and for prevention of

restenosis. Alternatively the resulting coated particles may be placed into a conventional seed container, for example a titanium, glass or polymer container, suitable for implantation or insertion as a brachytherapy source using known planning equipment and software.

Example 28
Deposition of Palladium Iodide on a Variety of Substrates

The method cited in Example 5 applied to a variety of substrates as listed here:

a. Nylon beads
b. Molecular sieves (zeolites)
c. Clays (magnesium and aluminium silicates)
d. Glass beads
e. Anion exchange resins

The basic procedure was to first rotate the particles in a solution of $PdCl_2$ and then expose them to a solution of KI. The order was reversed for the anion exchange resin. All the samples showed some degree of coating except the glass beads. In general, exposure to the palladium solution caused a marked darkening of the particle surface indicating the binding of palladium ions. Subsequent exposure to KI produced a black coloured particle, indicating precipitation of PdI_2 onto the particle surface.

Example 29
Preparation of a titanium seed suitable for brachytherapy using $^{103}Pd^{125}I_2$ precipitated onto hydroxyapatite as the radioactive source

Twenty milliliters of a saturated solution of radioactive (103)palladium chloride ($^{103}PdCl_2$) is added to

one gram of 0.5 mm hydroxyapatite particles and rotated for one hour. The particles are filtered and thoroughly rinsed through a 500 mesh metal screen with water. The mixture is then placed into a 150-ml beaker with a stir bar. The excess solution is decanted off, leaving the particles still slightly wet. Thirty-five milliliters of a 0.5 M solution of radioactive potassium (125) iodide ($K^{125}I$) is then added and the mixture is stirred for fifteen minutes. The product is filtered and thoroughly rinsed through a 500 mesh metal screen with water and finally nanopure water. The particles are then bottled in nanopure water.

After rotating in the (103) palladium solution for one hour, the particles turn from white to brown. The addition of potassium (125) iodide causes the particles to turn dark brown as expected for the formation of the nearly black palladium iodide.

The resulting particles are placed into a conventional titanium seed container which has been plasma arc welded at one end. By analogy with the conventional seeds prepared using ^{125}I adsorbed onto ion exchange resin beads, these 0.5 mm particles are placed 4 to a container. The container top is then crimped and welded shut to make the resulting seed suitable for use in brachytherapy.

Levels of radioactivity are controlled through dilution of the radioactive ions with "cold" ions for complete coating of the beads. Thus the levels of radioactivity may be adjusted from as low as 0.1 millicurie/seed to over 10 millicuries/seed although generally, 0.4 to 2 millicuries/seed is desired for prostate cancer treatment. Higher levels of activity/seed may be achieved by using much smaller hydroxyapatite beads with increased surface area and hence greater amounts of $^{103}Pd^{125}I_2$ coating. Such seeds may be suitable for prevention or treatment of restenosis.

Claims

1. A radioactive source suitable for use in brachytherapy comprising one or more insoluble salts wherein the insoluble salt contains, or the insoluble salts together contain, at least two different radioisotopes.

2. A radioactive source as claimed in claim 1 wherein a single insoluble salt comprising at least two different radioisotopes is used.

3. A radioactive source as claimed in claim 2 wherein an anion and a cation of the salt each comprise at least one radioisotope.

4. A radioactive source as claimed in any of claims 1 to 3 wherein the radioisotopes emit different types or energies of radiation or have different half-lives.

5. A radioactive source as claimed in any of claims 1 to 4 wherein the insoluble salt includes ^{125}I, ^{103}Pd, ^{89}Sr, ^{35}S or ^{32}P.

6. A radioactive source as claimed in any of claims 1 to 5 wherein the insoluble salt is $^{103}Pd(^{125}I)_2$, $^{103}Pd^{35}S$, $^{89}Sr^{32}PO_4$ or $^{89}Sr^{35}SO_4$.

7. A radioactive source as claimed in any of claims 1 to 6 where one of the radioisotopes possesses at least one gamma emission with an energy suitable for external imaging outside the human body.

8. A radioactive source as claimed in any of claims 1 to 7 further comprising a suitable non-radioactive support material for the insoluble salt(s).

9. A radioactive source as claimed in any of claims 1 to 8 when the source is sealed within a biocompatible container.

10. An insoluble salt suitable for use in brachytherapy which comprises two or more different radioisotopes, with the proviso that the salt is not a pyrophosphate salt.

11. An insoluble salt as claimed in claim 10 which is $^{103}Pd(^{125}I)_2$, $^{89}Sr^{32}PO_4$, $^{89}Sr^{35}SO_4$ or $^{103}Pd^{35}S$.

12. A radioactive composition which comprises an insoluble salt as claimed in any of claims 10 or 11 together with a suitable non-radioactive support.

13. A method for the preparation of an insoluble salt as claimed in claim 10 or claim 11 which comprises:

(a) providing a solution of a suitable radioactive salt-forming anion,

(b) providing a solution of a corresponding radioactive salt-forming cation,

(c) mixing the solutions of the anion and cation together so that precipitation of the insoluble salt occurs.

14. A method for the preparation of a composition as claimed in claim 12 which comprises carrying out step (c) of claim 13 in the presence of a suitable non-radioactive support.

15. A method of treatment of a condition which is responsive to radiation therapy, which comprises the temporary or permanent placement of a radioactive source comprising one or more insoluble salts, wherein the insoluble salt contains, or the insoluble salts together

contain, at least two different radioisotopes, at the site to be treated within a patient for a sufficient period of time to deliver a therapeutically effective dose, and with the proviso that such salts are not pyrophosphate salts.

16. A method as claimed in claim 15 wherein the radioisotopes emit different types or energies of radiation or have different half-lives.

17. A method as claimed in any of claims 15 or claim 16 for the treatment of cancer, arthritis or restenosis.

18. A method as claimed in any of claims 15 to 17 for the treatment of prostate cancer or to inhibit restenosis.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/GB 99/03774

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K51/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE MEDLINE 'Online! US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US WISNER E R ET AL: "Contrast-enhancement properties of irradiated normal lymph nodes: initial experience with interstitially delivered iodinated nanoparticles." retrieved from STN Database accession no. 1998221847 XP002134177 abstract & ACADEMIC RADIOLOGY, (1998 APR) 5 SUPPL 1 S180-2;DISCUSSION S183-4. , ——	1-18

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 March 2000	10/04/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Berte, M

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Form PCT/ISA/210 (second sheet) (July 1992)

Interna al Application No
PCT/GB 99/03774

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE MEDLINE 'Online! US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US SERAFINI A N: "Current status of systemic intravenous radiopharmaceuticals for the treatment of painful metastatic bone disease." retrieved from STN Database accession no. 95049763 XP002134178 abstract & INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY, BIOLOGY, PHYSICS, (1994 DEC 1) 30 (5) 1187-94. REF: 70 ,	1,3,5,6, 10,11
A	US 5 674 177 A (FEHSENFELD PETER ET AL) 7 October 1997 (1997-10-07) cited in the application claims	1-18
Y	US 3 663 685 A (EVANS ROGER L) 16 May 1972 (1972-05-16) claims	1-18
P,X	WO 99 33766 A (COMMISSARIAT ENERGIE ATOMIQUE ;LACOUT JEAN LOUIS (FR); CARPENA JOE) 8 July 1999 (1999-07-08) page 7, line 7 - line 27; claims page 9, line 28 -page 10, line 28; claims 1,4,15	1
A	US 4 505 888 A (MOORE HERBERT ET AL) 19 March 1985 (1985-03-19) claims	
X	WO 97 19706 A (IBT TECHNOLOGY PARTNERS ;RUSSELL JOHN L JR (US); CONIGLIONE ROY (U) 5 June 1997 (1997-06-05) page 18, line 12 - line 32; claims	1-18
Y	WO 97 01304 A (MALLINCKRODT MEDICAL INC) 16 January 1997 (1997-01-16)	1-18
X	claims	1
P,X	WO 99 42177 A (RADIANCE MEDICAL SYSTEMS INC) 26 August 1999 (1999-08-26) page 14, line 8 - line 12; claims 1,3	1-18

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/03774

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 15-18 is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern al Application No
PCT/GB 99/03774

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5674177 A	07-10-1997	DE 4315002 C	18-08-1994
		AT 151620 T	15-05-1997
		WO 9426205 A	24-11-1994
		EP 0696906 A	21-02-1996
		JP 2735689 B	02-04-1998
		JP 8508436 T	10-09-1996
US 3663685 A	16-05-1972	CA 927281 A	29-05-1973
		CH 518720 A	15-02-1972
		DE 1916704 A	06-11-1969
		FR 2005279 A	12-12-1969
		GB 1269383 A	06-04-1972
		JP 50019604 B	08-07-1975
		SE 372421 B	23-12-1974
		SE 412313 B	03-03-1980
		US RE29066 E	07-12-1976
		US B451438 I	02-03-1976
WO 9933766 A	08-07-1999	FR 2772746 A	25-06-1999
US 4505888 A	19-03-1985	NONE	
WO 9719706 A	05-06-1997	AU 1407397 A	19-06-1997
		EP 0863771 A	16-09-1998
WO 9701304 A	16-01-1997	NONE	
WO 9942177 A	26-08-1999	AU 2687299 A	06-09-1999
		AU 2870499 A	06-09-1999
		WO 9942163 A	26-08-1999